base. Patients with an echo performed within 7 days of admission (n=227) were included in this analysis. Acute physiology (APACHE II) scores, used as a marker of illness severity, and heart failure (CHF) by Framingham criteria were determined retrospectively. Differences in clinical, microbiologic and echo variables between patients who died during index hospitalization and those who survived to discharge were assessed by univariable analysis. Logistic regression analysis was used to determine characteristics independently associated with in-hospital mortality.
Results: Patients with IE had a median age of 60±16 years. There were 100 (44%) women. 76 (33%) had diabetes mellitus (DM), 64 (28%) were on hemodialysis, and 44 (19%) had prosthetic valves. Median duration of symptoms prior to admission was 4 days, and CHF was present in 73 (32%). 54 (24%) patients underwent cardiac surgery during index hospitalization. Compared to patients who survived to discharge (n=186), patients who died during admission (n=41, 18%) were similar with respect to CHF, echo findings, embolic events and rate of surgery. In contrast, patients that died were more likely to have DM (56% vs. 28%), higher median APACHE II score (17 vs. 11), S. aureus infection (77% vs. 33%), and persistent bacteremia (39% vs. 16%) (p<0.05 for each). In multivariable analysis, only DM (OR 2.6, 95% CI 1.2-5.7) and S. aureus infection (OR 3.1, 95% CI 1.2-7.8) were independently associated with in-hospital mortality.
Conclusion: Controlling for severity of illness, the early predictors of mortality in IE are the presence of DM and S.aureus infection. These results suggest a role for host-pathogen factors in identifying patients at high risk for mortality who may be targeted for aggressive care.

1:48 p.m.

### 1109MP-172 Left-Sided Valvular Disease in Carcinoid Syndrome: Underestimation Without Repetitive Echocardiographies

Nicolas Mansencal, Franck Digne, Emmanuel Mitry, Jean-François Forissier, Thierry Joseph, Pascal Lacombe, Guillaume Jondeau, Philippe Rougier, Olivier Dubourg, Hôpital Ambroise Paré, Boulogne, France

Background: Right-sided valvular disease is well known in carcinoid syndrome but little is known about the left-sided valvular disease. The aim of our study was to assess the incidence of both right and left-sided valvular diseases and to determine the role of patent foramen ovale (PFO) with this left-sided valvular disease.
Methods: Sixty-three consecutive trans-thoracic echocardiographies (TTE) have been performed in 26 pts (mean age 59 ± 8 years, 54% women) presenting with carcinoid syndrome. The echocardiographic following parameters were assessed: 1) right-sided valvular disease, 2) left-sided valvular disease, 3) right to left shunting through a patent foramen ovale (PFO +) using contrast echocardiography at rest and after cough test or Vasalva maneuver.
Results: Mean follow-up was 21 ± 20 months. At control, TTE revealed 7 pts (27%) with right-sided valvular carcinoid disease (RVCD), 3 pts (12%) with left-sided valvular carcinoid disease (LVCD) and 8 PFO + (31%). At the end of follow-up, the incidence of RVCD, LVCD and PFO + was 38% (10 pts), 31% (8 pts) and 38% (10 pts) respectively. All patients with RVCD and PFO + (7 patients) exhibited progression or new appearance of left-sided valvular disease. Six patients (75%) had both LVCD and PFO +.
Conclusion: According to follow-up, our data suggest that the incidence of left-sided valvular injury might be underestimated in carcinoid syndrome without repetitive echocardiographies. PFO + resulting in right to left shunting seems to be a major factor of left-sided valvular injury and should be systematically researched in carcinoid syndrome.

## ORAL CONTRIBUTIONS

# 824FO Featured Oral Session...Emerging Concepts in Calcific Aortic Valve Stenosis

Monday, March 31, 2003, 2:00 p.m.-3:30 p.m.
McCormick Place, Room S403

2:15 p.m.

### 824FO-2 Atorvastatin Inhibits Aortic Valve Calcification in an Experimental Model of Chronic Hypercholesterolemia via Nonlipid Lowering Effects

Nalini M. Rajamannan, Malayannan Subramaniam, Margaret Springett, Marek Neikrasz, Stuart R. Stock, Konstantine I. Ignatiev, Joseph McConnell, Ravinder Singh, Neil Stone, Robert O. Bonow, Thomas C. Spelsberg, Northwestern University, Chicago, IL, Mayo Clinic, Rochester, MN

Intro: Calcific aortic valve disease is the third most common indication for aortic valve (AV) replacement in the USA. To further understand the cellular mechanisms of calcific aortic stenosis, we tested a model of chronic experimental hypercholesterolemia for calcification and also the non-lipid lowering effects of atorvastatin in the AV. Methods: Rabbits (n=48) were treated for 3 months: Group I: normal diet, Group II: 0.5% (w/w) chol diet, and Group III: 0.5% (w/w) chol diet + atorv (3mg/kg/day). Masson Trichrome (MT) stain was performed for mineralization. Serum chol and high-sensitivity C-reactive protein (hsCRP) levels were obtained by standard assays. Serum nitrite levels were measured with a nitric oxide analyzer. Immunoblots and immunohistochemistry were performed to measure the eNOS protein. MicroCT scans were performed for evaluation of calcification in the AV. Results: There was an increase in chol, hsCRP and calcification in Group II AV compared to Group I. Atorv inhibited calcification in the AV as assessed by micro-CT. Serum nitrite levels, eNOS protein expression (3-fold) and eNOS localization were decreased in Group II AV and increased in the Group III. MT stain demonstrated mineralization in the Group II AV. Concl: This finding of calcification in the AV during chronic experimental hypercholesterolemia provides evidence of bone mineralization in the aortic valve. Furthermore, this bone mineralization is inhibited by atorv and may be mediated by anti-inflammatory effects of atorv.

| | Group I | Group II | Group III |
|---|---|---|---|
| Chol (mg/dl) | 45±5.6 | 1726± 637* | 1088±503 |
| hsCRP (mg/dl) | 0.03±0.005 | 0.41±0.19 * | 0.04± 0.04** |
| Nitrites (nM) | 994.67+/-392.51 | 198.17+/-108.83*** | 745+/-340.79** |

2:30 p.m.

### 824FO-3 Tumor Necrosis Factor Alpha Induces Calcification of Aortic Valve Myofibroblasts

Jens J. Kaden Aslihan Sarikoc, Refika Kilic, Karl K. Haase, Carl-Erik Dempfle, Martin Borggrefe, University Hospital Mannheim, Mannheim, Germany

**Background:** Tumor necrosis factor alpha (TNF) induces calcification of arterial smooth muscle cells in vitro. Calcific aortic stenosis, the most prevalent heart valve disease in the elderly, is characterized by massive tissue calcification. We have shown recently that TNF is upregulated in stenotic aortic valves, and that it is associated with the remodeling of the extracellular matrix in this disorder. The influence of TNF on the pathogenesis of valvular calcification is unknown.
**Methods:** Human aortic valve myofibroblasts were isolated from explanted aortic valves. Confluent cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, 50 mg/mL ascorbic acid, and 50 mmol/L beta-glycerophosphate, with and without 100 ng/mL TNF. After 21 days, calcified cell nodules were counted. In total cell lysates, the expression of bone-type alkaline phosphatase and osteocalcin were assessed by immunoassay, alkaline phosphatase activity was measured by a kinetic assay, and calcium concentrations were determined by the cresolphthalein complexone method.
**Results:** Cells treated with TNF showed a 19-fold increase in nodule formation as compared to control. In cell lysates, incubation with TNF resulted in a 20-fold increase in bone-type alkaline phosphatase expression, a 7-fold increase in osteocalcin expression, a 3-fold increase in alkaline phosphatase activity and a 3-fold increase in calcium concentration as compared to control.
**Conclusion:** TNF induces an osteoblast-like phenotype in cultured human aortic valve myofibroblasts in vitro, as indicated by increased nodule formation, expression of osteoblast-associated genes and calcification. These results suggest that valvular calcification in calcific aortic stenosis may be actively regulated, involving an inflammatory process. This could could be a potential target for modification of valvular calcification in calcific aortic stenosis.

2:45 p.m.

### 824FO-4 Relation of Aortic Valve Calcification With Cardiovascular Risk Factors and Antiinflammatory Gene Polymorphisms in Patients With Degenerative Calcific Aortic Stenosis

Jan R. Ortlepp Fabian Schmitz, Vera Mevissen, Stephan Weiß, Richard Dronskowski, Klaus Zerres, Christian Weber, Rüdiger Autschbach, Bruno Messmer, Peter Hanrath, Rainer Hoffmann, University Hospital of Aachen, Aachen, Germany, Institute of Inorganic Chemistry, RWTH Aachen, Aachen, Germany

Background: Calcification of the aortic valve might be influenced by the prevalence of cardiovascular risk factors (CRF), whereas the influence of genetic factors remains uncertain.
Methods: [Ca5 (PO4)3OH] of 190 excised aortic valves with degenerative calcific aortic stenosis was determined using calcium atomic absorption analysis. Left heart catheterization, assessment of CRF and genotyping of the antiinflammatory interleukin 10 and chemokine receptor CCR5 polymorphisms were performed.
Results: There was a positive correlation of calcification (quintiles) with the mean gradient across the aortic valve (44 ± 14, 52 ± 16, 54 ± 16, 61 ± 15, 68 ± 19 mmHg; p<0.001). Males had a higher degree of calcification than females (26.2 ± 8.9 versus 20.6 ± 9.4 mass%; p<0.001), despite having the same mean gradient across the aortic valve (56 ± 17 versus 56 ± 19 mmHg; p=0.955). None of the investigated CRF was associated with the degree of calcification. Interleukin 10 promotor polymorphisms -1082, -819, and -592 were significantly associated with the degree of calcification (haplotypes: 17.9 ± 9.0 versus 24.5 ± 8.3 versus 25.4 ± 9.4 mass%; p<0.001). This was pronounced if certain allele carriers had also the CCR5 D32 allele (haplotypes plus CCR5: 17.9 ± 9.0 versus 24.5 ± 8.5 versus 27.5 ± 10.9 mass%; p<0.001).
Conclusion: CRF do not determine the amount of aortic valve calcification. However, gender and genetic polymorphism of the interleukin 10 and CCR5 gene are associated with the degree of aortic valve calcification.